2. SYNOPSIS

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Title of Study: A randomised, double-blind, placebo-controlled study to evaluate if rasagiline can improve depressive symptoms and cognitive function in non-demented, idiopathic Parkinson's disease patients ACCORDO Study (AzileCt® in Cognitive-impairment Related Depression).

Investigators: The study had a total of 12 investigators. The co-ordinating investigator for the study was [redacted]

Study Centres: The study was conducted at 12 Italian centres.

Publication (reference): None

Studied Period: First Subject Enrolled: 05-Mar-2010 Last Subject Completed: 02-Jul-2012	**Phase of Development**: Phase 4

Objectives:

Primary objective:

- To evaluate if rasagiline compared to placebo improves depressive symptoms as evaluated by the Beck Depression Inventory Amended (BDI-IA) total score over a treatment period of 12 weeks.

Secondary objectives were:

- To evaluate if rasagiline compared to placebo improves cognitive function, over a treatment period of 12 weeks, in idiopathic Parkinson's disease (PD) subjects. Cognition

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was assessed by using a formal neuropsychiatric cognitive test battery: Noun and Verb Naming Tasks (ENPA), Trail Making Test A & B (TMT A & B), Cognitive Performance Test (CPT), Stroop Test (ST), Clock Drawing Test (CDT), Rey Auditory Verbal Learning Test (RAVLT), Benton Judgment of Line Orientation Test (BJLOT), and Rey–Osterrieth Complex Figure (ROCF).

- To evaluate change in quality of life (QoL) following a treatment period of 12 weeks by using the Parkinson's Disease Questionnaire (PDQ-39) scale.
- To evaluate change in apathy following a treatment period of 12 weeks by using the Apathy Scale (AS).
- To evaluate change in mentation, behaviour, and mood, activities of daily living (ADL), motor function and complication of therapy following a treatment period of 12 weeks by using UPDRS scales Part I, Part II, Part III and Part IV, respectively.

Methods: This was a multicentre, national (one country), randomised, double-blind, placebo-controlled study conducted in 12 Italian centres in subjects with Parkinson's disease. Subjects were screened by use of the BDI-IA to define depression severity. Subjects were recruited from the Movement Disorders Outpatient Clinics from academic and hospital institutions in Italy. Only subjects with a BDI-IA score ≥ 15 at baseline were enrolled and randomly assigned (1:1) to rasagiline 1 mg/day or to placebo for 12 weeks.

Subjects had to be under stable treatment with dopaminergic agents at least 4 weeks before baseline. The recruitment period lasted up to 12 months. Each subject was treated for 3 months. The protocol assessments were performed by visits at baseline, Week 4, and at the end of the study, at 12 weeks. At Week 4, only depression BDI-IA, UPDRS (Part II and Part III only), adverse events (AEs)/recent and concomitant medication, and investigational medicinal product

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(IMP) returned/accountability assessments were performed.

Number of Subjects (planned and analysed):

Planned: 136 subjects; 68 subjects for each treatment group (1:1 rasagiline and placebo) were planned to be enrolled.

Actual: 123 subjects were randomized; 58 subjects in the active group and 65 subjects in the placebo group. The randomization was blocked at the site level before reaching the planned number of subjects as the sites could not enroll the planned number of subjects even though enrolment was extended multiple times.

Completed: 106 subjects

Analysed: 123 subjects with at least 1 dose of rasagiline or placebo were considered under the all-patients-treated set (APTS)/safety population. A total of 116 subjects, 53 subjects in rasagiline and 63 subjects in placebo, who had at least 1 valid post-baseline assessment of the primary efficacy variable were considered under the full-analysis set [FAS].

Diagnosis and Main Criteria for Inclusion: Subjects who met the following main criteria were included in the study:

- Between ≥ 40 and <80 years of age
- Diagnosed with idiopathic PD according to the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria for Parkinson’s disease for the clinical diagnosis of PD
- Depressive symptoms with a minimum severity of ≥ 15 using the BDI-IA and Hoehn and Yahr stage I-III

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- Under stable treatment with dopaminergic agents (4 weeks before baseline) without significant motor complications such as "on-off" phenomena and/or dyskinesia

Test Product, Dose, Mode of Administration, and Batch Number(s): Rasagiline (H. Lundbeck A/S [HLu] IMP), 1 mg, administered orally, once daily for 12 weeks, Batch number°R14269

Duration of Treatment: 12 weeks

Reference Therapy, Dose, Mode of Administration, and Batch Number(s): Matching placebo: 1 tablet/day, Batch number: PLR001

Criteria for Evaluation

Efficacy: The primary efficacy assessment was the BDI-IA. The primary efficacy endpoint was the change from baseline in BDI-IA total score.

Secondary efficacy assessments, listed below, were primarily to analyse the change from baseline in the following:

- Cognitive tests battery: ENPA, TMT A & B, CPT, ST, CDT, RAVLT, BJLOT, and ROCF
- QoL as evaluated by PDQ-39
- Apathy total score evaluated by AS
- UPDRS Part I to IV

As part of exploratory analyses, changes in BDI-IA scores were planned to be correlated to changes in cognitive tests, QoL, and UPDRS Part III scores in individual subjects during

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analysis.

Safety: Safety assessments included dermatologic assessments, laboratory assessments (hematologic and clinical chemistry), vital signs measurements, electrocardiogram (ECG), and assessments of AEs and withdrawals due to AEs.

Statistical Methods: The primary endpoint for this study was the clinical response after 12 weeks of treatment, defined as a change in total score from baseline depressive symptoms as measured by the BDI-IA total score. Depressive symptoms and cognitive assessments were performed at baseline, Week 4, and at the end of the study, at Week 12. In the absence of assessments following discontinuation, the Week 4 values were utilized if the score was available. Missing individual item scores in an otherwise complete multi-item assessment were approached through appropriate imputation techniques in the approach for multilevel regression modeling defined within the statistical analysis plan (SAP).

The comparison, between the two groups, of BDI-IA total score absolute change from baseline to Visit 3 (Week 12), was analysed by an analysis of covariance (ANCOVA) method, fitting the baseline value of BDI-IA as covariate and centre as a fixed factor. A centre-pooling algorithm, if applicable, was defined within the SAP prior to unblinding. Centre as a categorical variable and centre by treatment interactions was evaluated descriptively. In case the assumption of normally distributed data was grossly violated, the analysis of the primary efficacy parameter was conducted by means of a non-parametric method (Wilcoxon Rank-Sum Test).

For all the secondary efficacy parameters, the statistical analysis considered principally the changes from baseline to Week 12. The effect of the two treatment groups for secondary measures was analysed by means of the same method of the primary efficacy analysis. The following standardised parameters were analysed by the respective tests:

- Cognition:

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- Language: ENPA
- Attention: Trails B
- Frontal/executive functions: Scores of phonologic fluency for each of the three letters of the alphabet (F, A, and S), phonologic fluency scores for each of the semantic category (colours, animals, fruits, and cities and towns), ST, and CDT
- Memory: RAVLT
- Visuospatial: BJLOT and ROCF

- Quality of life: PDQ-39
- Apathy: AS
- UPDRS Part I, II, III, and IV: mentation, behaviour, mood, complications of therapy, ADL, and motor function

Changes in BDI-IA score were correlated to changes in cognitive tests, QoL, and UPDRS Part III scores in individual subjects through details as provided in the analysis plan document.

In addition to the efficacy analysis planned per protocol, the primary and secondary endpoints were also analysed excluding centre 11. This was done as it was clear after analyzing the primary efficacy endpoint, BDI-IA scores, that there was a centre effect, ie, 1 centre had a different performance than the other. Therefore, data were analysed excluding centre 11 in order to see if results would become significant; which was not the case comprehended after analysis. These have been presented as post hoc efficacy analysis in the clinical study report.

Few additional analysis (UPDRS Part I, II, and III single items, PDQ-39 single domain score, UPDRS II and III, UPDRS I and II and III, Equivalent scores and z scores for neuropsychiatric cognitive test battery, Hoehn & Yahr staging, Schwab and England ADL) were performed,

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though not planned per protocol/SAP, and presented in detail in the statistical analysis report (SAR).

The safety analysis was conducted on the APTS population. No inferential analysis of safety data was planned.

Results

Subject Disposition: A total of 123 subjects, 58 subjects in active treatment and 65 subjects in placebo were randomized into the study and administered at least 1 dose of rasagiline or placebo. Of the 123 enrolled subjects, 106 completed the study and 17 discontinued prematurely from the study.

Efficacy Results:

The primary endpoint of this study was the clinical response after 12 weeks of treatment, defined as a change from baseline in the BDI-IA total score.

The comparison, between the two treatment groups, of BDI-IA total score change from baseline to Visit 3 (Week 12), was analysed by an ANCOVA method, fitting baseline BDI-IA as covariate and centre as a fixed factor. Centre as a categorical variable and centre by treatment interactions was also evaluated descriptively. Correction for the baseline BDI-IA score and for the centre effects was performed as ANCOVA model # 1 and correction for the baseline BDI-IA score and for treatment effects was performed as ANCOVA model # 2. For the BDI-IA scores, a correction for the baseline BDI-IA score, the centre effects, and the withdrawal subjects was also performed as ANCOVA model # 3. All the models have been presented in detail in the SAR.

Primary efficacy endpoint - Depression: After 12 weeks of treatment there was no statistically significant difference (p=0.384) between the BDI-IA score reduction in the placebo group and in the rasagiline group. The difference of the BDI-IA score reduction between the two groups

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remained non-significant on performing a correction for the baseline score and for the centre and treatment effects. However, after 4 weeks of treatment, there was a statistically significant difference (p=0.035) between the BDI-IA score reduction in the placebo group and in the rasagiline group, which remained statistically significant on performing a correction for the baseline score and for the centre and treatment effects.

Secondary endpoints:

Similar to the primary efficacy endpoint, the comparison of change in individual secondary endpoints' scores from baseline to Visit 3 (Week 12) between the two treatment groups, was analysed by ANCOVA method, fitting baseline secondary endpoints as covariate and centre as a fixed factor. Centre as a categorical variable and centre by treatment interactions was also evaluated descriptively. Correction for the individual secondary endpoints' baseline score and for the centre effects was performed as an ANCOVA model and correction for the individual secondary endpoints' baseline score and for treatment effects was performed as an ANCOVA model. All the models for the above listed secondary endpoints have been presented in detail in the SAR. A summary of the same is presented in the following sections.

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S1: Secondary Endpoint Analysis Results:

Secondary Endpoints	**Total score change from baseline to Week 12 between the two groups (p-value)**	**Correction for the baseline score as covariate and for the treatment and centre as fixed factors (p-value)**	**Correction for the baseline score as covariate and treatment as fixed factor (p-value)**
Noun and Verb Naming Tasks (ENPA)	0.674	0.693	0.396
Trail Making Test A and B			
TMT A	0.338	0.550	0.660
TMT B	0.507	0.997	0.545
TMT B-A	0.431	0.854	0.467
Cognitive Performance Test			
CPT-L	0.115	0.324	0.206
CPT-C	0.519	0.847	0.521
Stroop Test			
ST-WR correct	0.870	0.528	0.575
ST-WR errors	0.652	0.801	0.930
ST-CN correct	0.205	0.453	0.178
ST-CN errors	0.212	0.781	0.186
ST-NC correct	0.924	0.841	0.775
ST-NC errors	0.029*	0.346	0.129
Clock Drawing Test	0.605	0.999	0.410
Rey Auditory Verbal Learning Test			
RAVLT-I	0.487	0.386	0.302
RAVLT D	0.526	0.949	0.764

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Benton Judgment of line Orientation Test	0.897	0.959	0.513
Rey-Osterrieth Complex Figure	0.512	0.799	0.715
QoL – PDQ-39	0.441	0.125	0.074
Apathy Scale	0.073	0.115	0.124
Unified Parkinson's Disease Rating Scale (ON)			
UPDRS-I (12 Weeks)	0.083	0.043*	0.030*
UPDRS-II (12 Weeks)	0.005*	0.024*	0.003*
UPDRS-III (12 Weeks)	0.162	0.062	0.090
UPDRS-II (4 Weeks)	0.358	0.214	0.262
UPDRS-III (4 Weeks)	0.162	0.071	0.082

UPDRS Part I: evaluation of mentation (mental activity or state of mind) or cognition (ability to acquire knowledge), behaviour and mood

UPDRS Part II: self-evaluation of the ADL including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, cutting food

UPDRS Part III: evaluation of motor function

Abbreviations: ADL = activities of daily life; CPT = Cognitive Performance Test; ENPA = Noun and Verb Naming Tasks; PDQ-39 = Parkinson's Disease Questionnaire-39; QoL = quality of life; RAVLT D = Rey Auditory Verbal Learning Test - delayed recall; RAVLT-I = Rey Auditory Verbal Learning Test – immediate recall; ST-CN = Stroop Test-colour naming; ST-NC = Stroop Test – non-congruent; ST-WR = Stroop Test – word reading;TMT = Trail Making Test; UPDRS = Unified Parkinson's Disease Rating

*Statistically significant

Cognition: After 12 weeks of treatment, in the formal neuropsychiatric cognitive test battery (ENPA, TMT A and B, CPT, Stroop Test, CDT, RAVLT, BJLOT, and ROCF), no statistically significant difference was noted between the test scores change in the placebo group and in the rasagiline, except for the ST-NC errors score, which failed to remain statistically significant upon performing a correction for centre and treatment effects.

PDQ-39 Scale (QoL) and Apathy Scale: The PDQ-39 score reduction (QoL assessment) and the change in the AS scores in the placebo group and in the rasagiline group was also found to be

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statistically non-significant after 12 weeks of treatments. No change in the statistical significance for QoL or AS was noted on performing a correction for the baseline score and for the centre and treatment effects.

UPDRS I, II and III: After 12 weeks of treatment, there was no statistically significant difference between the UPDRS-I ON (p=0.083) and UPDRS-III ON (p=0.162) score reduction in the placebo group and in the rasagiline group. However, a statistically significant difference, favouring rasagiline group, was noted between the UPDRS-II ON (p=0.005), UPDRS-II and III ON (p=0.013), and UPDRS-I, II and III ON (p=0.012) score reduction between the placebo group and in the rasagiline.

On performing a correction for the baseline UPDRS-I score and for the centre effects (p=0.043) and for the treatment effects (p=0.030), the difference in the score reduction between the two treatment groups becomes statistically significant. No change in the statistical significance was noted for other scores on performing a correction for the baseline score and for the centre and treatment effects.

Safety Results:

Safety population was represented by a total of 123 subjects (all subjects randomized, 58 in the active treatment and 65 in the placebo group). Fifteen subjects (25.9%) in the rasagiline group and 17 subjects (26.2%) in the placebo group had at least 1 treatment-emergent adverse event (TEAE) reported during the study; regardless of the relationship to the study drug.

Thirteen drug related (possibly or probably related) TEAEs were reported in the rasagiline group and 18 drug related (possibly or probably related) TEAEs in the placebo group.

Four subjects in the rasagiline group discontinued the study due to 4 distinct TEAEs (vertigo, nausea, dyskinesia, and left trunk flexion due to PD). None of the subjects in the placebo group discontinued the study due to a TEAE.

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A serious adverse event (SAE) of radius fracture and melanocytic naevus were reported in 2 subjects in the rasagiline group, while 1 subject in the placebo group had an event of polyneuropathy in malignant disease and respiratory disorder, both events were considered to be serious. None of the SAEs reported during the study were considered to be drug related.

All TEAEs and SAEs, except polyneuropathy in malignant disease, resolved with or without medical intervention, prior to the end of the study.

No clinically significant vital sign measurements, ECGs, or physical examinations findings were reported during the study.

Treatment emergent adverse events, laboratory abnormalities, vital sign measurements, ECGs, or physical examination did not show any clear trend with administration of rasagiline compared to placebo.

Conclusions: In non-demented, idiopathic PD subjects with at least mild to moderate depression (BDI-IA ≥15 at screening), rasagiline did not show evidence in improving depressive symptoms in comparison to concurrent placebo treatment as evaluated by the BDI-IA score over a treatment period of 12 weeks. However, at 4 weeks, rasagiline demonstrated statistically significant differences in BDI –IA score reduction compared to the placebo group ($p = 0.035$).

A number of secondary efficacy analyses were completed which add dimensions to the interpretation of the clinical effect, touching upon aspects of cognition, QoL, apathy, ADL as well as motor function improvement. These data suggest no consistent differences between rasagiline compared to placebo across a range of assessments of cognitive function over a period of 12 weeks in idiopathic Parkinson's disease subjects. Similarly, changes in QoL following a treatment period of 12 weeks using the PDQ-39 yielded non-significant results. However, data obtained from the UPDRS subscales may suggest an effect on various elements of mood, behaviour, and ADL when interpreted in the context of an exploratory trial.

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Specifically UPDRS I, II total change scores were statistically significantly different from placebo at endpoint (12 weeks) with evidence of maturation of an effect from Weeks 4 to 12. On performing a correction for the baseline UPDRS-I score and for the centre effects and for the treatment effects, the difference in the score reduction between the two treatment groups becomes statistically significant; no change in the statistical significance was noted for other scores on performing a correction for the baseline score and for the centre and treatment effects. These data suggest rasagiline related benefits compared to placebo in evaluation of mentation, behaviour, and mood (UPDRS I) and in self-evaluation of the activities of daily life (UPDRS II). Moreover, a statistically significant difference was noted between the UPDRS-II and III ON; and UPDRS-I, II and III ON score reduction between the placebo group and the rasagiline group, which remained statistically significant following appropriate adjustments to biostatistical models. In isolation, changes in the UPDRS III total score from baseline by treatment were not statistically significant suggesting the absence of consistent effects on clinician rated motor performance within the limitation of the sample size and duration of exposure.

The AS total score demonstrated effects nominally favouring rasagiline versus placebo at 12 weeks post treatment, although results were not statistically significant.

Except for the non-drug related SAEs, no major or clinically significant safety findings were noted during the study. No trends in the safety observations related to rasagiline treatment were observed.

Although the primary objective of this study was not met, results generate hypotheses suggesting treatment specific effect of rasagiline compared to placebo on mood including depressive symptomatology in subjects with idiopathic PD following 12 weeks of exposure. Results are both assessment and model dependent but in the context of an exploratory study; provide impetus for further development/clinical evaluations of rasagiline in subjects with Parkinson's disease that have a clinically important mood disturbance.

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